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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,400	06/22/2005	Stanton L. Gerson	CWR-7784PCT/US	7253

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EXAMINER	
PACKARD, BENJAMIN J	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,400	GERSON ET AL.	
	Examiner	Art Unit	
	Benjamin Packard	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,60,64,65,75,77,78 and 98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,59-62,64,65,67,75,77,78,83,85,88,98,101,103-106,111,113,172 and 203-233.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,61,62,67,83,85,88,101,103-106,111,113,172 and 230-233.

DETAILED ACTION

Applicants' arguments, filed 10/15/08, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions Change

Because Applicants cancelled references to the species under examination, i.e. PARP inhibitors, examination of the BER inhibitor is now extended to caffeine, a DNA polymerase inhibitor and methoxyamine, an AP endonulease inhibitor.

Claims 230-233 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, specifically, the elected anticancer agent was temozolomide, elected 09/28/07, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 09/28/07.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 59, 60, 64, 75, 77, and 98 were/are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention, specifically rejecting the term "AP endonuclease inhibitors".

This rejection is maintained.

Applicants assert with regards to the "AP endonuclease inhibitors" written description previously that they were in possession of "AP endonuclease inhibitors" and the Office failed to establish a prima facie case that the specification does not satisfy the written description requirement.

While Applicants do relate the functional language of AP endonuclease inhibitor to methoxyamine, N-ethylmaleimide, O^6-benzylguanin and compound of formula (1) at page 18 of the specification that relationship is not found in all the instant claims. It is noted that the disclosure of general compounds cited by Applicants at pg 19 of the specification are directed to compounds "that may possess AP endonuclease inhibitory activity". Where activity was not known, Applicant was not in possession of knowledge of whether these compounds would have the requisite inhibitory activity. While Applicants argue the specification discloses a method of identifying additional AP endonuclease inhibitors, Univ. of Rochester v. G.D. Searle, supra, stands for the proposition that the ability to find compounds based on a functional property, even when the method of determining the same is clearly disclosed, does not meet the written description requirement. Where there appears to be no disclosure of the broader class of compounds which have the requisite inhibitor activity, Applicants have not presented a sufficient number of species to reflect the potential variation within the broader genus.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59, 60, 64, 65, 75, 77, 78, and 98 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a method of potentiating a therapeutic effect of temozolamide by combination with methoxyamine (MX), does not reasonably provide enablement for treating the broader method of potentiating a therapeutic effect of anticancer agents which induce formation of AP sites by combination with base excision repair inhibitors.

This rejection is maintained.

Applicants assert there are known anticancer agents which treat various cancers which function at least in part by forming AP sites of DNA. Then Applicants point to the specification which discloses BER inhibitors can be used to potentate the effect of anticancer agents. Finally, Applicants assert the Examiner has not met the burden of presenting evidence to doubt the objective truth of Applicants statements.

In response to the working Examples, Applicant has submitted only a limited number of working examples, where the only evidence is directed to MX with TMZ, PD 128763 with TMZ, and O^6benzylguanin (BG) with TMZ. Then Applicants extrapolate some mechanism, postulating that mechanism is what is causing the effect, and then claiming the genus of compounds based on the mechanism. While such reasoning may be sufficient, Examiner rebuts such an argument with Cramer (US 4,325,950), which

discloses a BER inhibitor, caffeine (see instant spec at pg 21 line 10), while showing increased cell death in cell cultures with cis-$Pt(NH_3)_2Cl_2$, is not reasonably correlated to vivo testing (col 1 lines 13-29). Where there is a lack of predictability in the art, one of ordinary skill in the art would not readily accept the assertion that there will be a potentiated therapeutic effect, which is reasonably interpreted to include treatment in vivo) of an anticancer agent when administered with a BER inhibitor. Where such unpredictability exists, the testing required would be extensive, requiring testing each combination of anti-cancer treatments with each BER inhibitor in each possible cancer, with no reasonable expectation of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59, 60, 75, and 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Cramer (US 4,325,950).

Cramer teaches caffeine, an inhibitor of DNA repair, has been shown in cell culture studies to greatly increase cell kill caused by cis-$Pt(NH_3)_2Cl_2$ (col 1 lines 13-29).

Applicants define caffeine as a DNA polymerase inhibitor (instant specification pg 21 lines 6-10) and cis-$Pt(NH_3)_2Cl_2$ as an AP endoclulease inhibitor with is an alkylating cancer agent (instant specification pg 4 lines 25-27). Whether those classifications were

recognized or not, the same drugs were use to potentate an effect of the anticancer agent where the term "therapeutic" is interpreted broadly to include in vitro effects.

Claims 59, 60, 64, 65, 75, 77, 78, and 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Fortini et al (Carcinogenesis vol. 13 no. 1 (1992) pp.87-93).

Fortini et al teaches methoxyamine provides protection from the cytotoxicity of Sn1 alkylating agents (pg 91 Discussion, first few lines), where such are administered together.

Note, the potentiating effect would appear to be inherent given the same class of anticancer agents, alkylating agents, instantly claimed is administered with the same BER inhibitor, methoxyamine.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 59, 60, 64, 65, 75, 77, 78 and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fortini et al (Carcinogenesis vol. 13 no. 1 (1992) pp.87-93).

The reference is believed to be anticipatory as discussed above. For the sake of completeness of prosecution, purely arguendo and with regard to this particular ground of rejection only, however, it will be presumed that the prior art differs from the instant claims insofar as it does not specifically disclose actual in vivo results. If that is so, it would have been obvious as Fortini et al not only shows in vitro effects, but also mimics in vivo testing by incubating oligonucleotides simultaneously with MX and cell extract (pg 91 first full paragraph). Where such modeling is presented with evidence of effectiveness, one of ordinary skill in the art would have an expectation of success and minimal testing would be required to confirm the mimicked in vivo testing.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-R 8-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612